Kaohsiung Journal of Medical Sciences (2015) 31, 223–228

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.kjms-online.com

REVIEW ARTICLE

# Advances in upper airway cough syndrome

**Li Yu, Xianghuai Xu, Hanjing Lv, Zhongmin Qiu***

*Department of Respiratory Medicine, Tongji Hospital, Tongji University School of Medicine, Shanghai, China*

Received 31 October 2014; accepted 19 January 2015
Available online 4 March 2015

**KEYWORDS**
Airway inflammation;
Atopic cough;
Cough hypersensitivity syndrome;
Sinobronchial syndrome;
Upper airway cough syndrome

**Abstract** Upper airway cough syndrome (UACS), previously referred to as postnasal drip syndrome, is one of the most common causes of chronic cough. However, the pathogenesis of UACS/postnasal drip syndrome remains unclear, and physicians in countries throughout the world have different definitions and ways of treating this disease. The various proposed pathogeneses of UACS include the early postnasal drip theory, subsequent chronic airway inflammation theory, and a recent sensory neural hypersensitivity theory. Additionally, some researchers suggest that UACS is a clinical phenotype of cough hypersensitivity syndrome. While the general principles involved in treating UACS are similar throughout the world, the specific details of treatment differ. This review summarizes the various definitions, pathogenic mechanisms, treatments, and other aspects of UACS, to aid clinicians in expanding their knowledge of how to diagnose and treat this syndrome.


## Introduction

In 2006, the American College of Chest Physicians (ACCP) defined upper airway cough syndrome (UACS), previously referred to as postnasal drip syndrome (PNDS), as one of several critical pathogeneses of chronic cough [1,2]. In UACS patients, cough can be caused by a variety of upper respiratory disorders, including nasal and sinus diseases [3]. It can also result from anatomic abnormalities and physically or chemically-induced rhinitis, as well as pharyngeal diseases [4–6]. UACS/PNDS is the most common cause of chronic cough in the USA, and accounts for 24–52% of chronic coughs secondary to cough-variant asthma in China [2,7].

Although chronic cough can be effectively controlled in some patients, problems such as cough recurrence after drug withdrawal continue to occur. Additionally, UACS/PNDS is difficult to diagnose and treat because it often coexists with other disorders that contribute to chronic cough [8]. Finally, chronic cough can seriously affect a patient's quality of life, and even cause depressive symptoms [9].

Although UACS/PNDS has been proposed as a specific syndrome for > 100 years and become a severe clinical

Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Respiratory Medicine, Tongji Hospital, Tongji University School of Medicine, Number 389 Xincun Road, Shanghai 200065, China.
*E-mail address:* 96778@tongji.edu.cn (Z. Qiu).

http://dx.doi.org/10.1016/j.kjms.2015.01.005

problem, knowledge concerning its pathogenesis and management has remained inconsistent across different countries. This review summarizes the various aspects of UACS/PNDS.

## Concepts

PNDS was first mentioned by Frank in 1794, and later proved to be a common cause of chronic cough by Irwin et al [10] in the 1980s. Until recently, UACS has been regarded as a clinical diagnosis not supported by using specific objective methods of examination. In most cases, UACS has been diagnosed based on its clinical symptoms and the patient's response to treatment with an $H_1$ receptor antagonist. Some researchers support the still controversial idea of "silent PNDS", which stipulates that PNDS/UACS can be diagnosed when a cough is relieved with an $H_1$ receptor antagonist, even without the presence of relevant clinical manifestations [11]. Medical societies in several countries, including the USA, support the concept of PNDS/UACS.

The European Respiratory Society (ERS) characterizes postnasal drip as a symptom rather than a disease, and supports the premise that most patients with postnasal drip do not cough. Based on this premise, the ERS believes that postnasal drip cannot fully explain the cause of a cough, and does not accept a diagnosis of PNDS/UACS. Instead, PNDS/UACS is described as "rhinitis/rhinosinusitis" or "upper airway diseases-caused cough". While such diseases account for 6—21% of chronic cough cases in Europe, this prevalence is lower in the USA [6,10—12].

The Japanese Respiratory Society guidelines for management of cough indicate that UACS/PNDS is not a common etiology of chronic cough [13], and instead suggest sinobronchial syndrome (SBS) and atopic cough (AC) as the most common causes of chronic cough in Japan. SBS is characterized by a chronic cough caused by chronic rhinosinusitis, and its symptoms are effectively treated with 14- or 15-member ring macrolides and expectorants. AC is a disorder induced by atopic diseases, and its diagnostic criteria include one or more of the following findings, which suggest an atopic predisposition: (1) current or past history of an allergic disorder such as rhinitis, and other than asthma; (2) elevated peripheral blood eosinophils, increased serum total immunoglobulin E (IgE), positive for a specific IgE, positive allergen intradermal test, or elevated eosinophils in induced sputum. In reality, 80% of AC cases can be diagnosed as nonasthmatic eosinophilic bronchitis, and many other cases can be diagnosed as UACS according to the diagnostic criteria. Therefore, there is some overlap among SBS, AC, and UACS/PNDS, and the exact definition of each disorder remains to be determined. The relationships among UACS, AC, and SBS are shown in Fig. 1. Additionally, the guidelines provided by ACCP and ERS do not offer specific diagnostic criteria for AC and SBS, and in China, SBS and rhinitis induced chronic cough are both described as UACS/PNDS [3].

## Pathogenesis

Although the pathogenesis of UACS/PNDS is unclear, there are several theories, which are described below.

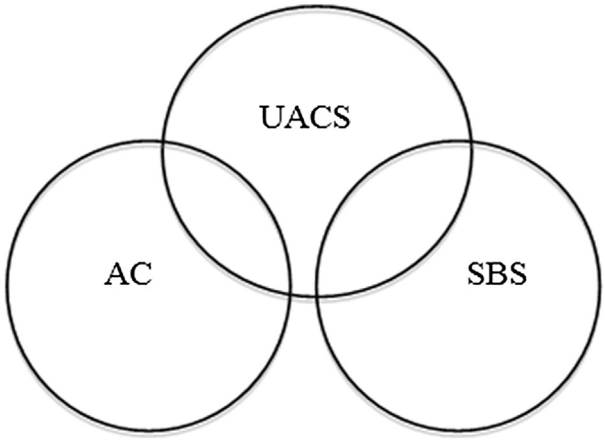


**Figure 1.** Relationships among upper airway cough syndrome (UACS), atopic cough (AC), and sinobronchial syndrome (SBS).

### Postnasal drip theory

In the past, chronic cough from UACS/PNDS was considered to result from postnasal drip-inducing mechanico- or chemostimulation of the afferent nerves innervating the pharynx, larynx, or lower airways [2,3]. Cho et al [14] found that cough sensitivity in some chronic coughers was closely related with extrathoracic airway responsiveness during capsaicin provocation. Thus, extrathoracic airway hyperresponsiveness irritated by postnasal drip might be a mechanism of cough.

However, postnasal drip and transport of nose and paranasal sinus mucous secretions to the pharynx or larynx are normal physiological processes. Bardin et al [15] placed a radionuclide in the maxillary sinus of sinusitis patients, and 24 hours later detected its presence in the maxillary sinus, nasopharynx, esophagus, and lower gastrointestinal tract; however, its presence was not detected in the pulmonary aspirate of any patient. The entire experimental process included the patient's sleep time, which is theoretically the most likely period of time for aspiration to occur. This study showed that, after 24 hours, secretions of the nasal sinus had barely entered the lower airways. O'Hara and Jones [16] followed up 108 consecutive rhinitis/rhinosinusitis patients who displayed symptoms of postnasal drip, and found that only 21% complained of cough. Among the patients with a cough, only 8% had postnasal drip and a cough with no other discernible pathology such as bronchiectasis, asthma, or sarcoidosis. These data indicate that cough is uncommon in patients with postnasal drip, and may not be associated with postnasal drip. Thus, a growing number of scholars now doubt the postnasal drip theory. Due to this uncertain causal relationship, starting in 2006, the ACCP has used the term UACS to replace PNDS [2].

### Airway inflammation

#### Lower airway inflammation theory

Recent studies have shown that lower airway inflammation is commonly associated with chronic cough. Multiple inflammatory mediators, including histamine and prostaglandins, can increase the sensibility of cough via

stimulating local nerve endings in the lower airways [17]. Furthermore, numerous studies have shown that airway inflammation in patients with nonasthmatic chronic cough, including patients with UACS, is mainly due to infiltration of mast cells, neutrophils, and lymphocytes, which is different from the etiologies associated with cough-variant asthma and eosinophilic bronchitis [18,19]. Niimi [20] reported that patients with UACS showed a remodeling of the airways, characterized by increased sub-basement membrane thickness, vascularity, vessel size, and signs of goblet cell hyperplasia. Additionally, the submucosal infiltration of mast cells in patients with nonasthmatic cough differed from the infiltration of eosinophils and neutrophils found in patients with asthmatic chronic cough. Therefore, Niimi [20] suggested that the airway structural changes or remodeling phenomena were the results of long-term airway inflammation. Our previous study showed that airway inflammation, which might be associated with activation of mast cells, could be a cause of increased cough sensitivity, ultimately leading to cough [19]. Ma et al [21] found increased levels of neurogenic inflammatory mediators in the supernatant fractions of induced sputum from UACS patients. They suggested that cough from UACS might be generated when cough receptors are stimulated by inflammatory mediators released from lower airways neurons, which were previously activated by a nervous reflex when the nerve endings in the nasal mucosa received an inflammatory stimulation. Additionally, some studies have demonstrated that patients with rhinitis have increased numbers of neurons capable of generating large amounts of neurogenic inflammatory mediators in their nasal mucosa [22]. However, further studies are needed to confirm whether such changes also occur in the lower airways.

One possible cause of lower airway inflammation is postnasal drip. Although most of the secretions do not enter the lower airways, older individuals and patients with cerebrovascular disease often have an impaired local swallowing reflex, and are susceptible to aspiration pneumonia. Therefore, one cannot exclude the possibility that an early stage of airway inflammation caused by aspiration might lead to increased cough sensitivity. A second possible cause of airway inflammation is mechanical stimulation. Some scholars believe that cough, as a repeated mechanical/physical stimulus, can damage airway mucosa and either cause or aggravate airway inflammation. This mechanical/physical stimulation might induce the airway epithelium to release multiple growth factors such as transforming growth factor β2, epidermal growth factor [23], and nerve growth factor, all of which are correlated with the upregulation of transient receptor potential vanilloid 1 (TRPV1) expression and increased cough sensitivity. Hara et al [24] developed a model of induced airway collapse similar to that involved in cough by applying a rapid negative pressure, and found that such mechanical stimulation produced an increased number of neutrophils in the airway and also increased cough-reflex sensitivity. Their study directly proved that cough can cause neutrophil-involved airway inflammation via mechanical stimulation. Airway inflammation may also exist as a localized manifestation of a systemic inflammatory response. It is well-known that some rhinitis patients, and especially those suffering from allergic rhinitis, have atopic manifestations such as increased serum IgE levels, positive intracutaneous test results, and eosinophilia in blood and sputum, which are associated with genetic factors [25]. In these patients, airway inflammation might exist as a local manifestation of a systemic inflammatory response. However, whether the inflammation is a cause or an effect of the chronic cough should be elucidated in future studies [20].

### Upper airway inflammation

Some otolaryngologists have proposed that UACS is not only associated with nasal diseases, but might also be influenced by a chronic inflammation in the pharynx or larynx, such as inflammations resulting from allergic pharyngitis and chronic tonsillitis [3,19]. Such inflammations may result from long-term contact with nasal or sinus secretions. Currently, only few clinical data have suggested that chronic tonsil hypertrophy in adults and children may be associated with cough that could be relieved or terminated following tonsillectomy [26]. Additional clinical studies are required to confirm the relationship between chronic cough and other diseases of the pharynx or larynx [2].

## Sensory neural hypersensitivity theory

### Activated nasal nerves and increased cough sensitivity

Pecova et al [27] reported increased cough sensitivity in allergic rhinitis patients without cough compared to sensitivity in healthy controls, and this difference was especially prominent during the pollen allergy season. Individuals with increased cough sensitivity are more easily impacted by internal and external environmental tussive stimuli or show an increased intensity of an existing cough. Thus, increased cough sensitivity as seen in allergic rhinitis patients may be one of the mechanisms that causes cough in UACS patients [27]. Histamine is an important inflammatory mediator, and directly stimulates sensory neurons. Capsaicin activates local nerves via combing with TRPV1 in nerve endings [28]. Although nasal inhalation of histamine or capsaicin does not produce cough in healthy controls or allergic rhinitis patients, it can increase cough sensitivity. Studies have shown that following stimulation of nasal sensory nerves with histamine or capsaicin, cough can be evoked by the oral inhalation of a certain concentration of aerosolized capsaicin [29]. The number of coughs increased 60—100% in a nasal stimulated group compared with a healthy control group, and similar results were obtained when studying healthy individuals, allergic rhinitis patients, or a guinea pig model. Moreover, the degree of inflammation found in the nasal mucosa was positively correlated with the presence of rhinitis-induced cough [28,30]. These studies verified that stimulation of nasal nerves might be the cause of elevated cough sensitivity.

The mechanism of nasal neural activation-elicited increased cough sensitivity is not clear. After accepting an external stimulus, the nasal mucosa produces a variety of inflammatory factors such as histamine. These factors stimulate nasal sensory nerves and also the nasociliary nerve of the trigeminal nerve, which conducts signals to the nucleus of the spinal trigeminal tract. The central area, which accepts the projection of the vagus nerve, is the

nucleus tractus solitaries (NTS). To determine whether there was cross-over between these two pathways, Plevková et al [31] used capsaicin to stimulate the nasal mucosa of guinea pigs, and, when compared with control animals, found increased expression of C-fos in both the brainstem NTS and trigeminal nerve. C-fos is expressed when activated neurons generate action potentials, indicating that neurons in two different locations are both activated [30]. It is speculated that in upper airway diseases, different central parts interact to influence the generation of cough through stimulation of nasal nerves [31,32]. Therefore, it is hypothesized that environmental stimuli elicit inflammation of the nasal mucosa, resulting in signals being transmitted to the nucleus of the spinal trigeminal tract, and partially to the NTS through the local trigeminal nerve. The NTS might also be activated by a discharge of neurons in the nucleus of the spinal trigeminal tract, which in turn, will signal the vagus nerve in the lower airways mucosa to generate neurogenic inflammation, resulting in increased cough sensitivity.

Most studies have focused on patients with allergic rhinitis, and there are few studies on patients with rhinosinusitis. Japanese guidelines for diagnosing various types of cough state that SBS patients have normal cough sensitivity and elevated levels of neutrophils in the secretions of their nose and lower airways [13]; however, these conclusions are not supported by data from clinical studies. Most studies on cough sensitivity have used the methods established by Fujimura et al [33]. In that procedure, capsaicin solution is used to detect the response of TRPV1 on C fibers, and this solution does not react with cough receptor Aδ fibers found in airways, which are mainly sensitive to mechanical stimuli. Further studies are needed to ascertain whether the higher sensitivity of Aδ fibers in SBS patients leads to cough, or whether the higher secretion levels in the airways of these patients prevent the capsaicin solution from combining with TRPV1 on C fibers.

**Increased neural sensitivity in the pharynx or larynx**

A constant postnasal drip can stimulate long-term chronic inflammation in the pharynx or larynx, resulting in localized inflammatory manifestations such as red and swollen mucosa; however, it is not clear if postnasal drip causes increased local sensitivity. Our recent study showed that cough sensitivity was decreased in UACS patients, rhinitis/rhinosinusitis patients without cough, and healthy controls following local anesthesia of nerve endings in the pharynx and larynx by lidocaine [34]. While there were no differences in the extent of the decreases, UACS patients still showed higher cough sensitivity than the other two groups following local anesthesia. Our data suggest that although cough receptors in the larynx were probably involved in the heightened cough sensitivity shown by UACS patients, local sensitivity was not significantly higher than in the other two groups, and was not the main cause of cough. Instead, stimulation of lower respiratory cough receptors to an excited state may have been the main cause for the increased cough sensitivity in UACS patients.

In the 1990s, Bucca et al [35] proposed the concept of larynx hyper-responsiveness (LHR), in which a human protective reflex—laryngeal chemical reflex can prevent a liquid substance from entering the lower airways. In healthy adults, this reflex can produce a cough that may be diagnosed as LHR, also designated as irritable larynx by Bucca et al [35]. In this condition, a $>$ 25% decrease in the maximal midinspiratory flow rate after inhalation of histamine is considered positive. Bucca et al's [36] recent study showed a 76% prevalence of LHR among UACS patients, which was higher than the prevalence among noncough patients, such as those with asthma. Bucca et al [36] believed that these patients had increased sensitivity in the pharynx and larynx, which made it easier to generate a cough after providing a stimulus.

**Cough hypersensitivity syndrome**

Morice [37] recently proposed the concept of cough hypersensitivity syndrome (CHS), and suggested that the majority of patients with chronic cough can be incorporated into this syndrome. Patients with CHS usually present with one of three different phenotypes: (1) patients with a predominant phenotype of rhinal symptoms (such as UACS); (2) patients with a Th2-cell dominant phenotype (cough-variant asthma or nonasthmatic eosinophilic bronchitis); and (3) patients with a predominant phenotype characterized by acid reflux and heartburn (gastroesophageal reflux cough). The CHS concept also conforms with the notion of sensory hyper-reactivity (SHR), defined as a state of increased sensory neural reactivity in patients with chronic cough, and first suggested by Millqvist [38], who proposed that increased cough sensitivity was a manifestation of SHR, and stated that patients with chronic cough appeared to have "airway hyperalgesia". Additionally, the increased sensory nerve sensitivity allowed even a minimal stimulation to cause a cough, which was included in the category of a sensory neuropathy [39]. It has been demonstrated that the pathological change associated with both SHR and cough hypersensitivity is the upregulation of TRPV1 expression in sensory nerves, and that TRPV1 antagonists are effective for improving the symptoms of SHR and decreasing cough sensitivity [40,41]. The cough demonstrated by UACS patients is due to hypersensitivity of the upper airways sensory nerve or lower airways sensory nerve, or a combination of both. Further studies are needed to clarify this mechanism.

## Treatments

The principal method for treating UACS is similar in different countries, and usually involves administration of antihistamines [2,3,5,6,13]. There are very few differences among the official guidelines for treating UACS in different countries (Table 1).

## Conclusion and expectations

In conclusion, UACS/PNDS is a clinical syndrome with a variety of causes, and proper treatment is associated with certain difficulties. The current treatments are limited, and some patients have problems of repeated relapse. However, an effective treatment may be found when the pathogenesis of the syndrome is further clarified. Recent studies have shown that higher than normal expression of specific sodium channels might be associated with the increased

**Table 1** Guidelines for treatment of upper airway cough syndrome in different countries and areas.

| | USA | UK | Europe | Australia | Japan | China |
|---|---|---|---|---|---|---|
| Allergic rhinitis | New-generation A + D | Nasal steroids | New-generation A + D | Nasal steroids +(A) | A | Nasal steroids + A; D (if necessity) |
| Nonallergic rhinitis | First-generation A + D | | | | | First-generation A + D |
| Chronic rhinosinusitis | First-generation A + D; Nasal steroids Antibiotic | | | Nasal steroids; Antibiotic (purulent) | Low dose of 14/15-member ring macrolide | Nasal steroids; First-generation A + D; Low dose of macrolide; Antibiotic |

A = antihistamine; D = decongestant.

cough sensitivity shown by UACS/PNDS patients. Further research should focus on whether cough sensitivity can be adjusted by controlling the expression of those specific sodium channels (1.7, 1.8, and 1.9), and whether such changes might improve symptoms in chronic cough patients [42].

## Acknowledgments

This study was partly supported by a grant from the National Natural Science Foundation of China (No. 81200065) and a grant for Development of Science and Technology from the Committee of Science and Technology of Shanghai (No. 12ZR1428300).

## References

[1] Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. Chest 1998;114:133S—81S.
[2] Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Chest 2006;129:63S—71S.
[3] Asthma Workgroup of Chinese Society of Respiratory Diseases (CSRD). Chinese Medical, Association The Chinese national guidelines of the diagnosis and management of cough. Chin J Tuberc Respir Dis 2009;32:407—13.
[4] Birring SS. Controversies in the evaluation and management of chronic cough. Am J Respir Crit Care Med 2011;183:708—15.
[5] Gibson PG, Chang AB, Glasgow NJ, Holmes PW, Katelaris P, Kemp AS, et al. CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian cough guidelines summary statement. Med J Aust 2010;192:265—71.
[6] Morice AH, Fontana GA, Sovijarvi AR, Pistolesi M, Chung KF, Widdicombe J, et al. The diagnosis and management of chronic cough. Eur Respir J 2004;24:481—92.
[7] Lai KF, Chen RC, Liu CL, Luo W, Zhong SQ, He MZ, et al. Etiology and a diagnostic protocol for patients with chronic cough. Zhonghua Jie He He Hu Xi Za Zhi 2006;29:96—9 [Article in Chinese].
[8] Weinberger M, Fischer A, editors. Differential diagnosis of chronic cough in children. Allergy and Asthma Proceedings. Providence: OceanSide Publications, Inc.; 2014.
[9] Dicpinigaitis PV, Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. Chest 2006; 130:1839—43.
[10] Sanu A, Eccles R. Postnasal drip syndrome. Two hundred years of controversy between UK and USA. Rhinology 2008;46: 86—91.
[11] Birring SS. New concepts in the management of chronic cough. Pulm Pharmacol Ther 2011;24:334—8.
[12] Saleh H. Rhinosinusitis, laryngopharyngeal reflux and cough: an ENT viewpoint. Pulm Pharmacol Ther 2009;22:127—9.
[13] Kohno S, Ishida T, Uchida Y, Kishimoto H, Sasaki H, Shioya T, et al. The Japanese Respiratory Society guidelines for management of cough. Respirology 2006;11(Suppl. 4):S135—86.
[14] Cho YS, Lee CK, Yoo B, Moon HB. Cough sensitivity and extrathoracic airway responsiveness to inhaled capsaicin in chronic cough patients. J Korean Med Sci 2002;17:616—20.
[15] Bardin PG, Van Heerden BB, Joubert JR. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. J Allergy Clin Immunol 1990;86:82—8.

[16] O'Hara J, Jones NS. "Post-nasal drip syndrome": most patients with purulent nasal secretions do not complain of chronic cough. Rhinology 2006;44:270—3.
[17] Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID. Induced sputum inflammatory mediator concentrations in chronic cough. Am J Respir Crit Care Med 2004;169:15—9.
[18] Birring SS, Brightling CE, Symon FA, Barlow SG, Wardlaw AJ, Pavord ID. Idiopathic chronic cough: association with organ specific autoimmune disease and bronchoalveolar lymphocytosis. Thorax 2003;58:1066—70.
[19] Shi CQ, Yu L, Wei WL, Huang Y, Lv HJ, Qiu ZM. Effect of airway inflammation on pathogenesis of upper airway cough syndrome. Chin J Resp Crit Care Med 2009;8:256—8 [Article in Chinese].
[20] Niimi A. Structural changes in the airways: cause or effect of chronic cough? Pulm Pharmacol Ther 2011;24:328—33.
[21] Ma HM, Liu SM, Lin MJ, Liu XY. Role of sensory neuropeptide in the chronic cough induced by postnasal drip syndrome. Chin J Pract Intern Med 2007;27:531—2.
[22] O'Hanlon S, Facer P, Simpson KD, Sandhu G, Saleh HA, Anand P. Neuronal markers in allergic rhinitis: expression and correlation with sensory testing. Laryngoscope 2007;117:1519—27.
[23] Irwin RS, Ownbey R, Cagle PT, Baker S, Fraire AE. Interpreting the histopathology of chronic cough: a prospective, controlled, comparative study. Chest 2006;130:362—70.
[24] Hara J, Fujimura M, Ueda A, Myou S, Oribe Y, Ohkura N, et al. Effect of pressure stress applied to the airway on cough-reflex sensitivity in Guinea pigs. Am J Respir Crit Care Med 2008;177:585—92.
[25] Wang de Y. Genetic predisposition for atopy and allergic rhinitis in the Singapore Chinese population. Asia Pac Allergy 2011;1:152—6.
[26] Birring SS, Passant C, Patel RB, Prudon B, Murty GE, Pavord ID. Chronic tonsillar enlargement and cough: preliminary evidence of a novel and treatable cause of chronic cough. Eur Respir J 2004;23:199—201.
[27] Pecova R, Zucha J, Pec M, Neuschlova M, Hanzel P, Tatar M. Cough reflex sensitivity testing in in seasonal allergic rhinitis patients and healthy volunteers. J Physiol Pharmacol 2008;59(Suppl. 6):557—64.
[28] Tatar M, Plevkova J, Brozmanova M, Pecova R, Kollarik M. Mechanisms of the cough associated with rhinosinusitis. Pulm Pharmacol Ther 2009;22:121—6.
[29] Plevkova J, Brozmanova M, Pecova R, Tatar M. The effects of nasal histamine challenge on cough reflex in healthy volunteers. Pulm Pharmacol Ther 2006;19:120—7.
[30] Brozmanova M, Bartos V, Plank L, Tatar M. Experimental allergic rhinitis-related cough and airway eosinophilia in sensitized guinea pigs. J Physiol Pharmacol 2007;58(Suppl. 5):57—65.
[31] Plevková J, Poliaček I, Adamkov M, Svirlochová K, Varga I. Brainstem neuronal populations activated in the model of ovalbumine induced allergic rhinitis in guinea pigs—the c-Fos study. Biologia 2011;66:922—7.
[32] Plevková J, Song WJ. Chronic cough in subjects with upper airway diseases - analysis of mechanisms and clinical applications. Asia Pac Allergy 2013;3:127—35.
[33] Fujimura M, Sakamoto S, Kamio Y, Matsuda T. Effects of methacholine induced bronchoconstriction and procaterol induced bronchodilation on cough receptor sensitivity to inhaled capsaicin and tartaric acid. Thorax 1992;47:441—5.
[34] Yu L, Xu X, Wang L, Yang Z, Lu H, Qiu Z. Capsaicin-sensitive cough receptors in lower airway are responsible for cough hypersensitivity in patients with upper airway cough syndrome. Med Sci Monit 2013;19:1095—101.
[35] Bucca C, Rolla G, Scappaticci E, Baldi S, Caria E, Oliva A. Histamine hyperresponsiveness of the extrathoracic airway in patients with asthmatic symptoms. Allergy 1991;46:147—53.
[36] Bucca CB, Bugiani M, Culla B, Guida G, Heffler E, Mietta S, et al. Chronic cough and irritable larynx. J Allergy Clin Immunol 2011;127:412—9.
[37] Morice AH. The cough hypersensitivity syndrome: a novel paradigm for understanding cough. Lung 2010;188(Suppl. 1):S87—90.
[38] Millqvist E. The airway sensory hyperreactivity syndrome. Pulm Pharmacol Ther 2011;24:263—6.
[39] Chung KF, McGarvey L, Mazzone SB. Chronic cough as a neuropathic disorder. Lancet Respir Med 2013;1:414—22.
[40] Gibson PG, Ryan NM. Cough pharmacotherapy: current and future status. Expert Opin Pharmacother 2011;12:1745—55.
[41] Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: A double-blind randomized controlled trial. J Allergy Clin Immunol 2014;134:56—62.
[42] Muroi Y, Ru F, Chou YL, Carr MJ, Undem BJ, Canning BJ. Selective inhibition of vagal afferent nerve pathways regulating cough using Nav 1.7 shRNA silencing in guinea pig nodose ganglia. Am J Physiol Regul Integr Comp Physiol 2013;304:R1017—23.